DEPARTMENT OF HEALTH & HUMAN SERVICES — Public Health Service

Memorandum

SEP 19 1996

Date

From: Director, Office of Device Evaluation (HFZ-400)
Center for Devices and Radiological Health (CDRH)

Subject: Premarket Approval of Xillix Technologies Corporation
Xillix LIFE-Lung Fluorescence Endoscopy System - ACTION

To: The Director, CDRH
ORA _____

ISSUE. Publication of a notice announcing approval of the subject PMA.

FACTS. Tab A contains a FEDERAL REGISTER notice announcing:

(1) a premarket approval order for the above referenced medical device (Tab B); and

(2) the availability of a summary of safety and effectiveness data for the device (Tab C).

RECOMMENDATION. I recommend that the notice be signed and published.

Susan Alpert, Ph.D., M.D.

Attachments
Tab A - Notice
Tab B - Order
Tab C - S & E Summary

DECISION

Approved _____ Disapproved _____ Date _____

Prepared by Kirby J. Cooper, CDRH, HFZ-470, 8/27/96, 594-2080

TAB A

A

DEPARTMENT OF HEALTH AND HUMAN SERVICES

DRAFT

FOOD AND DRUG ADMINISTRATION

[DOCKET NO. _____]

Xillix Technologies Corp.; PREMARKET APPROVAL OF Xillix LIFE-Lung Fluoresence Endoscopy System

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA) is announcing its approval of the application submitted by Hogan and Hartson, Washington, D.C., U.S. representative for Xillix Technologies Corp., Richmond, B.C., Canada, for premarket approval, under section 515 of the Federal Food, Drug, and Cosmetic Act (the act), of Xillix LIFE-Lung Fluoresence Endoscopy System. After reviewing the recommendation of the Ear, Nose, and Throat (ENT) Devices Panel, FDA's Center for Devices and Radiological Health (CDRH) notified the applicant, by letter on September 19, 1996, of the approval of the application.

DATES: Petitions for administrative review by (insert date 30 days after date of publication in the FEDERAL REGISTER). Written comments by (insert date 30 days after date of publication in the FEDERAL REGISTER).

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ADDRESSES: Written requests for copies of the summary of safety and effectiveness data and petitions for administrative review, to the Dockets Management Branch (HFA-305), Food and Drug Administration, 12420 Parklawn Drive, rm 1-23, Rockville, MD 20857.

FOR FURTHER INFORMATION CONTACT:

Kirby J. Cooper,

Center for Devices and Radiological Health (HFZ-470),

Food and Drug Administration,

9200 Corporate Blvd.,

Rockville, MD 20850,

301-594-2080.

SUPPLEMENTARY INFORMATION: On December 21, 1995, Hogan and Hartson, Washington D.C., U.S. representative for Xillix Technologies Corp., Richmond, B.C. Canada, submitted to CDRH an application for premarket approval of Xillix LIFE-Lung Fluorescence Endoscopy System. The device is a fluorescence endoscopy system and is indicated for use as an adjunct to white light bronchoscopy, using an Olympus BF-20D bronchoscope, to enhance the physician's ability to identify

and locate bronchial tissue, suspicious for moderate/severe dysplasia or worse, for biopsy and histologic evaluation in the following patient populations:

1. Patients with known or previously diagnosed lung cancer; and
2. Patients with suspected lung cancer including, (a) patients with Stage I completely resected lung cancer, with no evidence of metastatic disease, who are at risk for secondary disease, and (b) patients suspected of having lung cancer because of clinical symptoms such as positive sputum cytology, hemoptysis, unresolved pneumonia, persistent cough, or positive X-ray.

On June 11, 1996, the Ear, Nose, and Throat Devices Panel of the Medical Devices Advisory Committee, an FDA advisory panel, reviewed and recommended approval of the application.

On September 19, 1996, CDRH approved the application by a letter to the applicant from the Director of the Office of Device Evaluation, CDRH.

A summary of the safety and effectiveness data on which CDRH based its approval is on file in the Dockets Management Branch (address above) and is available from that office upon written request. Requests should be identified with the name of the device and the docket number found in brackets in the heading of this document.

Opportunity For Administrative Review

Section 515(d)(3) of the act (21 U.S.C. 360e(d)(3)) authorizes any interested person to petition, under section 515(g) of the act for administrative review of CDRH's decision to approve this application. A petitioner may request either a formal hearing under part 12 (21 CFR part 12) of FDA's administrative practices and procedures regulations or a review of the application and CDRH's action by an independent advisory committee of experts. A petition is to be in the form of a petition for reconsideration under §10.33(b) (21 CFR 10.33(b)). A petitioner shall identify the form of review requested (hearing or independent advisory committee) and shall submit with the petition supporting data and information showing that there is a genuine and substantial issue of material fact for

resolution through administrative review. After reviewing the petition, FDA will decide whether to grant or deny the petition and will publish a notice of its decision in the FEDERAL REGISTER. If FDA grants the petition, the notice will state the issue to be reviewed, the form of the review to be used, the persons who may participate in the review, the time and place where the review will occur, and other details.

Petitioners may, at any time on or before (insert date 30 days after date of publication in the FEDERAL REGISTER), file with the Dockets Management Branch (address above) two copies of each petition and supporting data and information, identified with the name of the device and the docket number found in brackets in the heading of this document. Received petitions may be seen in the office above between 9 a.m. and 4 p.m., Monday through Friday.

This notice is issued under the Federal Food, Drug, and Cosmetic Act (secs. 515(d), 520(h) (21 U.S.C. 360e(d), 360j(h))) and under authority delegated to the Commissioner of Food and Drugs (21 CFR 5.10) and redelegated to the Director, Center for Devices and Radiological Health (21 CFR 5.53).

Dated: _____.

_____

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
9200 Corporate Boulevard
Rockville MD 20850

SEP 19 1996

Barry Allen
Xillix Technologies Corporation
c/o Howard Holstein, Esq.
Hogan & Hartson
Columbia Square
555 Thirteenth Street, N.W.
Washington, D.C. 20004-1109

Re: P950042
Xillix LIFE-Lung Fluorescence Endoscopy System
Filed: December 22, 1995
Amended: March 5, 13, 21 and 25, 1996; April 18, 1996;
May 20 and 22, 1996; June 27, 1996; July 9, 1996;
and August 7 and 30, 1996.

Dear Mr. Allen:

The Center for Devices and Radiological Health (CDRH) of the Food and Drug Administration (FDA) has completed its review of your premarket approval application (PMA) for the Xillix LIFE-Lung Fluorescence Endoscopy System. This device is indicated for use as an adjunct to white light bronchoscopy, using an Olympus BF-20D bronchoscope, to enhance the physician's ability to identify and locate bronchial tissue, suspicious for moderate/severe dysplasia or worse, for biopsy and histologic evaluation in the following patient populations:

1. Patients with known or previously diagnosed lung cancer; and

2. Patients with suspected lung cancer including, (a) patients with Stage I completely resected lung cancer, with no evidence of metastatic disease, who are at risk for secondary disease, and (b) patients suspected of having lung cancer because of clinical symptoms such as positive sputum cytology, hemoptysis, unresolved pneumonia, persistent cough, or positive X-ray.

We are pleased to inform you that the PMA is approved subject to the conditions described below and in the "Conditions of Approval" (enclosed). You may begin commercial distribution of the device upon receipt of this letter.

The sale, distribution, and use of this device are restricted to prescription use in accordance with 21 CFR 801.109 within the meaning of section 520(e) of the Federal Food, Drug, and Cosmetic Act (the act) under the authority of section 515(d)(1)(B)(ii) of the act.

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FDA has also determined that to ensure the safe and effective use of the device that the device is further restricted within the meaning of section 520(e) under the authority of section 515(d)(1)(B)(ii), (1) insofar as the labeling specify the requirements that apply to the training of practitioners who may use the device as approved in this order and (2) insofar as the sale, distribution, and use must not violate sections 502(q) and (r) of the act.

In addition, FDA has concluded that adequate training is crucial for the effective use of the device by physicians. Therefore, FDA requires that the firm make available and maintain a training course and training materials for instructing physicians concerning the proper use of the fluorescence device and the images it produces.

In accordance with 21 CFR 814.44(e), FDA requires continuing evaluation of the effectiveness of the device in the form of a postmarket reproducibility study. The postapproval study will assess the ability of 32 physicians to determine the same classifications for 100 fluorescence images (3,200 total test readings) with agreement greater than or equal to 85%. The study must be conducted in adherence to the study design submitted as an amendment to the PMA and found acceptable by FDA. The study must be completed and all results provided in the form of a PMA postapproval report no later than two years from the date of approval of this PMA.

In addition to the postapproval requirements in the enclosure, postapproval reports including summaries of the progress of the postapproval study of reproducibility must be submitted at 6 months, 12 months, and 18 months from the date of the approval of this application, unless all reproducibility data from the postapproval study has already been submitted in final form prior to the two year deadline.

CDRH will publish a notice of its decision to approve your PMA in the FEDERAL REGISTER. The notice will state that a summary of the safety and effectiveness data upon which the approval is based is available to the public upon request. Within 30 days of publication of the notice of approval in the FEDERAL REGISTER, any interested person may seek review of this decision by requesting an opportunity for administrative review, either through a hearing or review by an independent advisory committee, under section 515(g) of the Federal Food, Drug, and Cosmetic Act (the act).

Failure to comply with the conditions of approval invalidates this approval order. Commercial distribution of a device that is not in compliance with these conditions is a violation of the act.

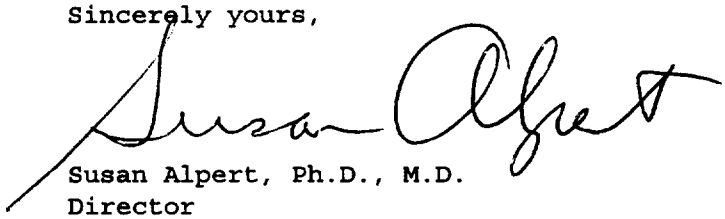
You are reminded that, as soon as possible and before commercial distribution of your device, you must submit an amendment to this PMA submission with copies of all approved labeling in final printed form.

All required documents should be submitted in triplicate, unless otherwise specified, to the address below and should reference the above PMA number to facilitate processing.

PMA Document Mail Center (HFZ-401)
Center for Devices and Radiological Health
Food and Drug Administration
9200 Corporate Blvd.
Rockville, Maryland 20850

If you have any questions concerning this approval order, please contact Mr. Kirby J. Cooper at (301) 594-2080.

Sincerely yours,



Susan Alpert, Ph.D., M.D.
Director
Office of Device Evaluation
Center for Devices and
Radiological Health

Enclosure

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Issued: 5-2-95

CONDITIONS OF APPROVAL

APPROVED LABELING. As soon as possible, and before commercial distribution of your device, submit three copies of an amendment to this PMA submission with copies of all approved labeling in final printed form to the PMA Document Mail Center (HFZ-401), Center for Devices and Radiological Health, Food and Drug Administration (FDA), 9200 Corporate Blvd., Rockville, Maryland 20850.

ADVERTISEMENT. No advertisement or other descriptive printed material issued by the applicant or private label distributor with respect to this device shall recommend or imply that the device may be used for any use that is not included in the FDA approved labeling for the device. If the FDA approval order has restricted the sale, distribution and use of the device to prescription use in accordance with 21 CFR 801.109 and specified that this restriction is being imposed in accordance with the provisions of section 520(e) of the act under the authority of section 515(d)(1)(B)(ii) of the act, all advertisements and other descriptive printed material issued by the applicant or distributor with respect to the device shall include a brief statement of the intended uses of the device and relevant warnings, precautions, side effects and contraindications.

PREMARKET APPROVAL APPLICATION (PMA) SUPPLEMENT. Before making any change affecting the safety or effectiveness of the device, submit a PMA supplement for review and approval by FDA unless the change is of a type for which a "Special PMA Supplement-Changes Being Effected" is permitted under 21 CFR 814.39(d) or an alternate submission is permitted in accordance with 21 CFR 814.39(e). A PMA supplement or alternate submission shall comply with applicable requirements under 21 CFR 814.39 of the final rule for Premarket Approval of Medical Devices.

All situations which require a PMA supplement cannot be briefly summarized, please consult the PMA regulation for further guidance. The guidance provided below is only for several key instances.

A PMA supplement must be submitted when unanticipated adverse effects, increases in the incidence of anticipated adverse effects, or device failures necessitate a labeling, manufacturing, or device modification.

A PMA supplement must be submitted if the device is to be modified and the modified device should be subjected to animal or laboratory or clinical testing designed to determine if the modified device remains safe and effective.

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A "Special PMA Supplement - Changes Being Effected" is limited to the labeling, quality control and manufacturing process changes specified under 21 CFR 814.39(d)(2). It allows for the **addition** of, but **not the replacement** of previously approved, quality control specifications and test methods. These changes may be implemented before FDA approval upon acknowledgment by FDA that the submission is being processed as a "Special PMA Supplement - Changes Being Effected." This acknowledgment is in addition to that issued by the PMA Document Mail Center for all PMA supplements submitted. **This procedure is not applicable to changes in device design, composition, specifications, circuitry, software or energy source.**

Alternate submissions permitted under 21 CFR 814.39(e) apply to changes that otherwise require approval of a PMA supplement before implementation of the change and include the use of a 30-day PMA supplement or annual postapproval report. FDA must have previously indicated in an advisory opinion to the affected industry or in correspondence with the applicant that the alternate submission is permitted for the change. Before such can occur, FDA and the PMA applicant**(s)** involved must agree upon any needed testing protocol, test results, reporting format, information to be reported, and the alternate submission to be used.

POSTAPPROVAL REPORTS. Continued approval of this PMA is contingent upon the submission of postapproval reports required under 21 CFR 814.84 at intervals of 1 year from the date of approval of the original PMA. Postapproval reports for supplements approved under the original PMA, if applicable, are to be included in the next and subsequent annual reports for the original PMA unless specified otherwise in the approval order for the PMA supplement. Two copies identified as "Annual Report" and bearing the applicable PMA reference number are to be submitted to the PMA Document Mail Center (HFZ-401), Center for Devices and Radiological Health, Food and Drug Administration, 9200 Corporate Blvd., Rockville, Maryland 20850. The postapproval report shall indicate the beginning and ending date of the period covered by the report and shall include the following information required by 21 CFR 814.84:

(1) Identification of changes described in 21 CFR 814.39(a) and changes required to be reported to FDA under 21 CFR 814.39(b).

(2) Bibliography and summary of the following information not previously submitted as part of the PMA and that is known to or reasonably should be known to the applicant:

(a) unpublished reports of data from any clinical investigations or nonclinical laboratory studies involving the device or related devices ("related" devices include devices which are the same or substantially similar to the applicant's device); and

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(b) reports in the scientific literature concerning the device.

If, after reviewing the bibliography and summary, FDA concludes that agency review of one or more of the above reports is required, the applicant shall submit two copies of each identified report when so notified by FDA.

ADVERSE REACTION AND DEVICE DEFECT REPORTING. As provided by 21 CFR 814.82(a)(9), FDA has determined that in order to provide continued reasonable assurance of the safety and effectiveness of the device, the applicant shall submit 3 copies of a written report identified, as applicable, as an "Adverse Reaction Report" or "Device Defect Report" to the PMA Document Mail Center (HFZ-401), Center for Devices and Radiological Health, Food and Drug Administration, 9200 Corporate Blvd., Rockville, Maryland 20850 within 10 days after the applicant receives or has knowledge of information concerning:

(1) A mixup of the device or its labeling with another article.

(2) Any adverse reaction, side effect, injury, toxicity, or sensitivity reaction that is attributable to the device and

(a) has not been addressed by the device's labeling or

(b) has been addressed by the device's labeling, but is occurring with unexpected severity or frequency.

(3) Any significant chemical, physical or other change or deterioration in the device or any failure of the device to meet the specifications established in the approved PMA that could not cause or contribute to death or serious injury but are not correctable by adjustments or other maintenance procedures described in the approved labeling. The report shall include a discussion of the applicant's assessment of the change, deterioration or failure and any proposed or implemented corrective action by the applicant. When such events are correctable by adjustments or other maintenance procedures described in the approved labeling, all such events known to the applicant shall be included in the Annual Report described under "Postapproval Reports" above unless specified otherwise in the conditions of approval to this PMA. This postapproval report shall appropriately categorize these events and include the number of reported and otherwise known instances of each category during the reporting period. Additional information regarding the events discussed above shall be submitted by the applicant when determined by FDA to be necessary to provide continued reasonable assurance of the safety and effectiveness of the device for its intended use.

REPORTING UNDER THE MEDICAL DEVICE REPORTING (MDR) REGULATION. The Medical Device Reporting (MDR) Regulation became effective on December 13, 1984, and requires that all manufacturers and importers of medical devices, including in vitro diagnostic devices, report to FDA whenever they receive or otherwise became aware of information that reasonably suggests that one of its marketed devices

(1) may have caused or contributed to a death or serious injury or

(2) has malfunctioned and that the device or any other device marketed by the manufacturer or importer would be likely to cause or contribute to a death or serious injury if the malfunction were to recur.

The same events subject to reporting under the MDR Regulation may also be subject to the above "Adverse Reaction and Device Defect Reporting" requirements in the "Conditions of Approval" for this PMA. FDA has determined that such duplicative reporting is unnecessary. Whenever an event involving a device is subject to reporting under both the MDR Regulation and the "Conditions of Approval" for this PMA, you shall submit the appropriate reports required by the MDR Regulation and identified with the PMA reference number to the following office:

Division of Surveillance Systems (HFZ-531)
Center for Devices and Radiological Health
Food and Drug Administration
1350 Piccard Drive, Room 240
Rockville, Maryland 20850
Telephone (301) 594-2735

Events included in periodic reports to the PMA that have also been reported under the MDR Regulation must be so identified in the periodic report to the PMA to prevent duplicative entry into FDA information systems.

Copies of the MDR Regulation and an FDA publication entitled, "An Overview of the Medical Device Reporting Regulation," are available by written request to the address below or by telephoning 1-800-638-2041.

Division of Small Manufacturers Assistance (HFZ-220)
Center for Devices and Radiological Health
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

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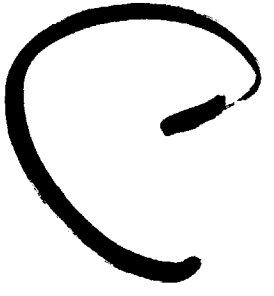


SUMMARY OF SAFETY AND EFFECTIVENESS DATA

I. GENERAL INFORMATION

Device Generic Name: Fluorescence Imaging System

Device Trade Name: Xillix LIFE - Lung Fluorescence Endoscopy System

Applicant's Name and Address:
Xillix Technologies Corp.
#300 - 13775 Commerce Parkway
Richmond, B.C. V6V 2V4 Canada

U.S. Representative:
Howard M. Holstein, Esq.
Hogan & Hartson, L.L.P.
555 Thirteenth Street, N.W.
Washington, DC. 20004

Premarket Approval Application (PMA) Number: P950042

Date of Panel Recommendation: June 11, 1996

Date of Notice of Approval to the Applicant: September 19, 1996

II. INDICATIONS FOR USE

The Xillix LIFE - Lung Fluorescence Endoscopy System is indicated for use as an adjunct to white light bronchoscopy (WLB), using an Olympus BF-20D bronchoscope, to enhance the physician's ability to identify and locate bronchial tissue, suspicious for moderate/severe dysplasia or worse, for biopsy and histologic evaluation in the following patient populations:

(1) Patients with known or previously diagnosed lung cancer; and

(2) Patients with suspected lung cancer including (a) patients with Stage I completely resected lung cancer, with no evidence of metastatic disease, who are at risk for secondary disease, and (b) patients suspected of having lung cancer because of clinical symptoms such as positive sputum cytology; hemoptysis, unresolved pneumonia, persistent cough, or positive X-ray.

III. DEVICE DESCRIPTION

Functional Description

The Xillix LIFE - Lung Fluorescence Endoscopy System utilizes a laser attached to a bronchoscope to elicit fluorescence in bronchial tissue with light centered at the 442-nm wavelength. Attenuation by the bronchoscope causes the light to be diffuse and low intensity when it reaches the tissue. The energy absorbed by the tissue causes the tissue to fluoresce. The device is used without the aid of drugs to enhance the fluorescence.

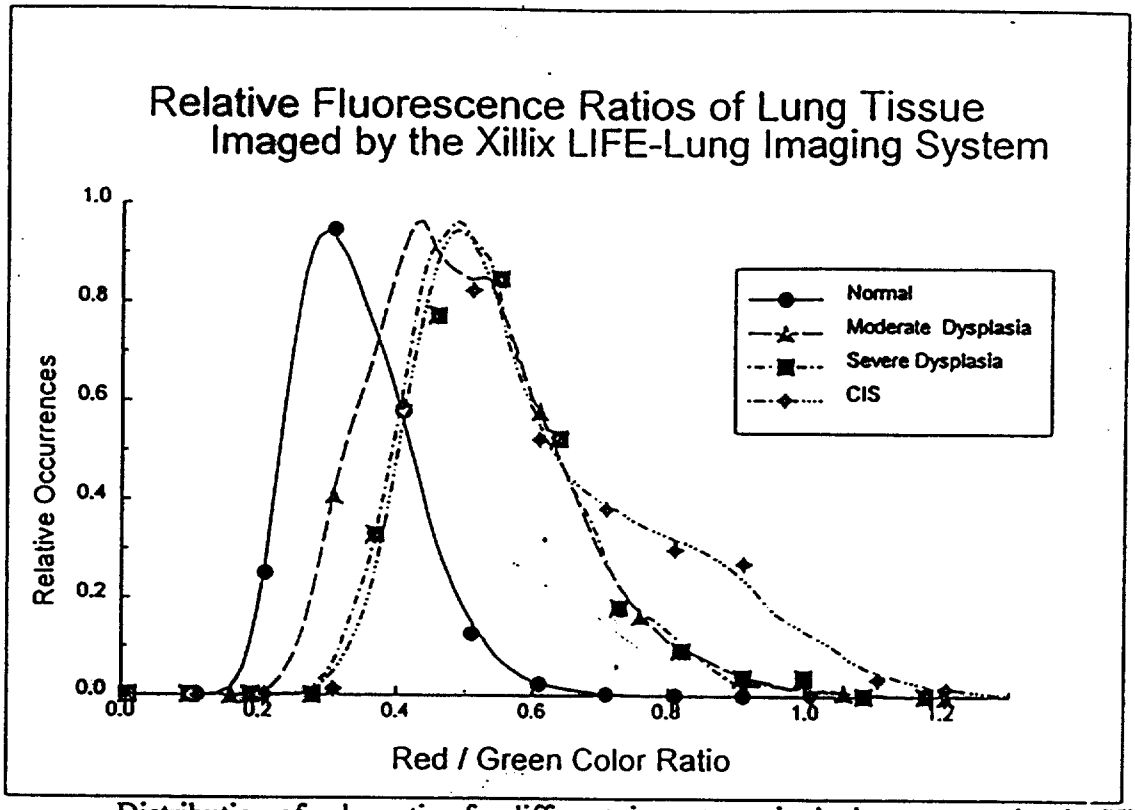
The very low intensity autofluorescence is captured by the fiber optics at the bronchoscope tip and is transmitted to the Xillix LIFE - Lung Fluorescence Endoscopy System camera housing which is attached to the optics of the bronchoscope. Within the housing, the light is split into two beams. One light beam is filtered so that only primarily red autofluorescent light remains. The other light beam is filtered so primarily green autofluorescent light is transmitted. The displayed image on the monitor is the ratio of the combined red and green autofluorescence signals. This is designed to compensate for variations in illumination within the field of view.

The low intensity red and green autofluorescent light beams are amplified by image intensifiers and then captured by two charge-coupled device (CCD) cameras. These cameras transform the light beams into electrical signals which can be digitized for storage in a computer. Software is used to maintain the original ratio of the red and green light intensities when the gain of the camera is adjusted by the user for increased brightness. The two signals are adjusted for non-linearity and converted into analog video signals which can be displayed in real time on a high-resolution monitor. The system has the capability of acquiring and displaying images at a rate of 30 images per second.

In-vivo spectroscopic measurements have shown that the green and red autofluorescence from abnormal tissue (moderate/severe dysplasia, carcinoma in situ (CIS), and invasive carcinoma) are similar in intensity; therefore, the resulting color mix on the monitor typically is perceived by the physician as brownish-red for suspicious areas. Similar spectroscopic measurements from normal tissue have demonstrated that the green autofluorescence intensity is significantly greater than the red autofluorescence intensity resulting in a displayed color mix which is typically perceived as green by the user. Bleeding or inflamed tissue will mask the autofluorescence or may cause normal tissue to be perceived as suspicious.

The determination of suspicious lung tissue for biopsy is based primarily on the perceived difference in hue for each bronchial area displayed on the monitor as the physician examines the airways. Figure 1 illustrates the relationship between the physiological condition of the tissue and the hue displayed by the device.

FIGURE 1



Distribution of color ratios for different tissue types in the lung as seen by the Xillix LIFE-Lung Imaging System.

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When suspicious areas are located, the physician can store the image digitally in the computer, labeling it with the general anatomical area. The stored images and videotape may be re-examined later when determining where to biopsy.

Components

The Xillix LIFE - Lung Fluorescence Endoscopy System is composed of five main components: Imaging Console, Illumination Console, Image Monitor, Image Camera, and Image Software.

(a) Imaging Console

The Imaging Console contains the subcomponents that control the image acquisition and data management processes. The Imaging Console consists of the following subcomponents: control screen, keyboard, S-VHS video cassette recorder, system processor, video printer, video I/O panel, and foot switch.

The operator uses the control screen and its custom graphical user interface to communicate with the system processor and control the functions of the Imaging Console. It is through the Imaging Console and the control screen that the operator is able to enter patient data, display, acquire and store images, obtain color prints, and videotape the procedure.

(b) Illumination Console

The Illumination Console contains a class IIIb helium-cadmium (HeCd) laser and power supply as the source of the blue light used to elicit autofluorescence. The He-Cd laser is capable of emitting up to 150 mW of blue light at 442.1 nm, and when the console is used in conjunction with an Olympus BF-20D bronchoscope, 15-30 mW of light is emitted from the tip of the bronchoscope.

In addition to the laser, the Illumination Console consists of the following subcomponents: light guide socket, control panel, light measurement port, emergency stop button, and remote interlock connector. The tip of the bronchoscope is routinely inserted into the light measurement port to check for adequate output power following system warmup. The control panel provides operator control of the HeCd laser light, including a selector switch for controlling the light emitted from the bronchoscope.

The Illumination Console contains the following safety features: (1) a light guide socket that contains a mechanical shutter which permits the emission of light only when the bronchoscope is connected; (2) a shutter

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dial, which gives the operator control of the emission of laser light (only when the bronchoscope is attached); and (3) an emergency stop button that will interrupt power to the laser, thus preventing the emission of light, if the button is activated during a procedure.

(c) Image Monitor

The Image Monitor is a 13-inch RGB monitor used to display the images acquired by the Xillix LIFE - Lung Fluorescence System.

(d) Image Camera

The Image Camera, model Type L2, is composed of two low-intensity light video CCD cameras, one for the (G) green channel and one for the (R) red channel. The cameras are used to produce video images. The camera housing also includes components for splitting, filtering, and image intensifying the low intensity autofluorescent light prior to input to the CCD cameras. The two cameras transduce the image into synchronized video signals, which are then transmitted through the video I/O panel into a video processor, and then displayed on the Image Monitor.

The Image Camera gain, or video signal amplification, can be controlled manually by pushing buttons on the hand switch connected to the Image Camera or by pushing buttons on the control screen.

(e) Image Software

The Xillix LIFE - Lung Fluorescence Endoscopy System software serves three main functions: controlling video signals; providing the user with the means of storing and retrieving patient data; and controlling subcomponents, such as video cassette recorder.

Interfaced with the Image Camera, software is used to control the gain of the Image Camera. To ensure that the ratio of the green and red channels remains constant following amplification, the software controls the gain, such that the G and R input signals are amplified linearly and in specific proportion.

The software also controls the storage and retrieval of digital and video images. The image software allows the operator to perform the following functions with the real-time video image: (a) to acquire the live video image and record the image using the S-VHS video cassette recorder; (b) to create a snapshot from the video image (digitize an image) and store it in

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a database; and (c) to select specific stored digital images and view them on the Image Monitor, or locate the section of videotape where an image has been recorded.

In addition, the Image software provides the capability of copying data to, and restoring data from, a digital tape cartridge, providing the user with a means of keeping records as long as they are required.

The imaging software allows the user to control the system's video cassette recorder functions, except the loading and ejecting tapes. The software provides information, such as the amount of space available on the current videotape, to the operator.

The Image software controls the operation of the video printer, allowing the operator to print hard copy snapshots of a particular image. The software monitors the video printer to ensure it is functioning properly at all times.

Device Usage

The physician initially performs a complete white light bronchoscopic examination of the tracheobronchial tree (IV generation bronchi) and identifies suspicious tissue for biopsy. Images of the suspicious tissue are recorded on videotape and stored digitally in the computer.

With the bronchoscope still in the patient, the user disconnects the white light source and video camera and installs the laser light source and the image camera from the Xillix LIFE-Lung Fluorescence Endoscopy System. The physician then repeats the examination by imaging autofluorescence, again looking for suspicious tissue. Images of tissue areas determined to be suspicious are stored digitally in the computer along with the general anatomical location. Biopsies can then be taken and are submitted for histologic evaluation.

IV. CONTRAINDICATIONS, WARNINGS, AND PRECAUTIONS

Contraindications

The Xillix LIFE-Lung Fluorescence Endoscopy System should not be used on the following patients:

1. Patients who are contraindicated for white light bronchoscopic examination include:

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- patients with uncontrolled hypertension (systolic pressure > 200 mmHg, diastolic pressure > 120 mmHg)
- patients with unstable angina
- patients with white blood count less than 2000 or greater than 20,000 and/or platelet count less than 50,000
- patients with known bleeding disorder or patients on anticoagulant therapy.

2. Patients who are contraindicated for fluorescence examination include:

- patients who have received fluorescent photosensitizing agents (hematoporphyrin derivatives) within three months prior to the procedure
- patients who are on or have received chemopreventive drugs (e.g. retinoic acid) within 3 months prior to the procedure
- patients who have received ionizing radiation treatment to the chest within six months prior to the procedure
- patients who have received cytotoxic chemotherapy agents systematically within six months prior to the procedure.

Warnings

1. The Xillix LIFE- Lung Fluorescence Endoscopy System is not indicated for use as a stand-alone diagnostic device and should not be used as such. The Xillix LIFE-Lung Fluorescence Endoscopy System must be used in conjunction with the Olympus BF-20D flexible fiber optic bronchoscope.

2. The physician should perform a complete white light bronchoscopy, then repeat the examination using fluorescence. Because blood may mask the autofluorescence image, the physician should perform the biopsy procedure, moving from distal to proximal, only after completing both examinations. All lesions categorized as Class III should be biopsied, whether they were found under white light bronchoscopy, fluorescence, or both.

3. The Xillix LIFE-Lung Florescence Endoscopy System is intended to identify and locate abnormal bronchial tissue for biopsy. All diagnoses are determined by histological review.

4. The Xillix LIFE-Lung Fluorescence Endoscopy System should not be used in conjunction with photosensitizing agents.

5. Patients on anticoagulant therapy should discontinue use prior to examination for the period of time specified by their physician.

6. Patients with known sensitivity to local anesthetic agents should be carefully assessed prior to being considered for this examination.

7. Physicians who have red/green color blindness should not attempt to use the Xillix device, because they will not be able to judge the gradations of color associated with normal and abnormal bronchial tissue.

Precautions

1. The Xillix LIFE - Lung Fluorescence Endoscopy System is restricted by Federal Law to be used only by physicians who have completed appropriate training in flexible fiber optic bronchoscopy and who have been trained in the use of the Xillix device. The physician should use his/her judgment and experience in interpreting the fluorescence images. For further information refer to Xillix LIFE-Lung Fluorescence Endoscopy System Clinical Information and Training Manual.

2. The Xillix LIFE-Lung Fluorescence Endoscopy System may show fluorescence images that could be incorrectly interpreted by the physician. Images that appear bronchoscopically positive may be caused by inflammation, scope or suction trauma, scar tissue, presence of photosensitizing agents, or chemopreventive agents. Images that appear bronchoscopically negative may not always accurately indicate the absence of abnormal tissue, i.e., not all abnormal bronchial tissue will be detected.

3. The physician may perform the biopsies in white light or fluorescence. For lesions less than 5 mm in diameter which are not visible under white light bronchoscopy, the physician should perform the biopsy under fluorescence mode.

4. The Xillix LIFE - Lung Fluorescence Endoscopy System provides a mechanism to store, label and retrieve a digital image, in fluorescence and white light, of the suspicious area. The stored images, site-labeling and the physician's observational skills help to ensure that the biopsy is taken from the correct site as with WLB. Since there is a small chance of error, i.e., biopsy taken from an incorrect site, caution should be exercised when relying on these stored images to target the biopsy. An error could lead to misdiagnosis of a patient if normal tissue is inadvertently biopsied instead of the targeted abnormal tissue.

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5. Safety and effectiveness in pregnant women have not been established.

6. The presence of acute pulmonary infection including bronchitis and pneumonia may increase the risks associated with bronchoscopy and the risk of obtaining false positive readings from this examination.

V. ALTERNATIVE PRACTICES OR PROCEDURES

Physicians use x-rays, magnetic resonance imaging, CT scans and white light bronchoscopy to assist them in locating lung cancer tumors.

Other diagnostic tests for lung cancer which are used in limited indications in conjunction with bronchoscopy include but are not limited to the following: fluoroscopy, thoracic needle aspiration, lymph node biopsy, thoracoscopy, and thoracotomy.

VI. MARKETING HISTORY

Xillix has marketed the Xillix LIFE - Lung Fluorescence Endoscopy System in Canada, France and Germany. The device has not been removed from the market for any reason related to the safety and effectiveness of the device.

VII. POTENTIAL ADVERSE EVENTS

The following adverse events were reported during the clinical evaluation of this device:

1. one incident of post-bronchoscopy bronchitis
2. one incident of hypoxemia, less than 50 % oxygen saturation
3. one incident of drug reaction to topical cocaine which was used to control excessive bleeding from a biopsy site in a 76-year-old female.

Additionally, potential adverse events with the use of the Xillix LIFE-Lung Fluorescence Endoscopy System may include the following events sometimes associated with standard bronchoscopic procedures:

- infection
- bleeding
- pneumothorax (lung collapse)

- hypoventilation (inadequate breathing occasionally requiring use of a mechanical ventilator)
- reaction to medications (including local and intravenous anesthetics, medications used to control biopsy site bleeding, anti-arrhythmics, etc.)
- arrhythmias (irregular heart beat)
- hypotension (low blood pressure)
- postoperative sore throat and/or bloody sputum
- death

Additional biopsies may be taken as a result of the fluorescence examination. All biopsies indicated by the Xillix LIFE - Lung Fluorescence Endoscopy System are endobronchial. The risks of complications from endobronchial biopsies are lower than the risks from transbronchial biopsy which have been estimated to be 1.0% (ref. 1). The risks are lower since the tissue is visible during the endobronchial procedure and the bronchial wall is not traversed. Also, the length of the fiber optic examination will be longer for the combined examinations than it is for standard bronchoscopy.

Patients for whom the device is indicated are those for whom standard bronchoscopic examination for known or suspected lung cancer is already indicated. Potential adverse events for the Xillix LIFE-Lung Fluorescence Endoscopy System, while similar to those of white light bronchoscopy, may be potentiated by the increased number of biopsies and increased examination time associated with use of the device (during the clinical trial, the average additional time needed for the Xillix LIFE - Lung Fluorescence Endoscopy System examination was 14 minutes).

The following potential safety concerns have also been considered:

- Tissue damage by the blue light ---- Analysis of the physics data indicated that the risk of tissue damage from exposure to the blue light from a fluorescence exam is less than that from exposure to white light used in a WLB procedure. However, the cumulative risk for the combined procedures should be slightly higher than the risk for WLB alone. Nonetheless, the overall risk is considered minimal.

- DNA damage ---- The blue light of 442 nm is not considered mutagenic.

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VIII. SUMMARY OF NONCLINICAL STUDIES

Microbiological, Toxicological, Immunological, and Biocompatibility Testing

The Xillix LIFE - Lung Fluorescence Endoscopy System in itself does not come in contact with the patient's tissues or bodily fluids. The system is only used externally in conjunction with the Olympus BF-20D flexible fiber optic bronchoscope, as an adjunct to white light bronchoscopy. Microbiological, toxicological, immunological, and biocompatibility studies were not considered relevant to the safety or effectiveness of the Xillix LIFE - Lung Fluorescence Endoscopy System and were not performed.

Radiation Safety and Bioeffects

(a) Absorption of Relevant Chromophores in the Lung

The safety of broad-band white-light bronchoscopy is well established. Using a spectroradiometer, the radiant exposure from the Xillix LIFE - Lung Fluorescence Endoscopy System at 442 nm was measured at a factor of about 1.4 - 2.4 times less than that from typical white light bronchoscopic devices for the wavelength range 400-500 nm.

In order to demonstrate that the lower-energy blue light used in the Xillix LIFE - Lung Fluorescence Endoscopy System is not absorbed at a higher rate by the chromophores in the lung than is the broad-band white light used in white-light bronchoscopy, the company performed the following analysis.

The radiant power from the Xillix LIFE - Lung Fluorescence Endoscopy System He-Cd laser was measured with an ophir power meter. The spectral radiant power from the white-light xenon source were measured with an EG & G optical multi-channel analyzer. The known energy absorption rates of relevant chromophores were taken from the literature (ref. 2, 3, 4, 5, 6). These values were used to compare the energy absorbed from the two light sources. Calculations were made of the energy absorbed by the chromophores found in lung tissue over the wavelength range 400-500 nm for the conventional white light bronchoscopic source and the He-Cd laser radiation at 442 nm. The chromophores considered include beta carotene: all trans, beta carotene: 9-cis, roseoflavin, riboflavin, 5-deazaflavin F420, P flavin, 8-OH.Riboflavin, 6-OH.Riboflavin, PR enzyme in XP12E cells, PR enzyme in HESM, PR enzyme from HESM, PR enzyme from fibroblasts, PR enzyme from leukocytes,

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deoxygenated hemoglobin, oxygenated hemoglobin, bilirubin, bilirubin with HSA, and typical hematoporphyrin.

The calculation, which takes into account the absorption of radiation as a function of wavelength, demonstrated that, except for deoxygenated hemoglobin, more energy was absorbed from the light source used in conventional white light bronchoscopy than that from the He-Cd laser used in the Xillix LIFE - Lung Fluorescence Endoscopy System.

In the case of deoxygenated hemoglobin, about 30% more energy was absorbed from the He-Cd laser used in the Xillix LIFE - Lung Fluorescence Endoscopy System than that from the white light source used in conventional bronchoscopy. Because of the limited penetration of 442 nm into tissue, it is highly unlikely that a significant amount of deoxygenated blood will be exposed. In addition, hemoglobin in the blood is a photo biologically inert compound (ref. 7). Thus, the higher absorption of deoxygenated hemoglobin associated with the Xillix LIFE-Lung Fluorescence Endoscopy System when compared to that for the light source used in conventional white light bronchoscopy appears to be non-significant.

(b) Monte-Carlo Simulations of Radiation Absorption in Tissue

The company used Monte-Carlo simulations to compare the light distribution in bronchial tissue of the laser radiation at 442 nm from the Xillix LIFE - Lung Fluorescence Endoscopy System He-Cd laser to that from the light source used in conventional white-light bronchoscopy over the wavelength range 400-500 nm. Light distribution and energy absorption (as a function of depth of tissue) was estimated using a tissue model and optical properties of tissue. It was concluded that the He-Cd laser had less absorption than that from the white light source used in conventional bronchoscopy. For these calculations, it was assumed that the He-Cd laser was operated at a power level of 30 mW, and the white light source had a measured power level of 43 mW over the wavelength range from 400-500 nm.

(c) Mutagenesis, DNA Damage and UV Effects

Based on the literature, the absorption spectrum of DNA ends at about 300 nm, well before the wavelength of 442 nm of the He-Cd laser used in the Xillix LIFE - Lung Fluorescence Endoscopy System. No damage from optical radiation effects is anticipated at the 442 nm laser wavelength since action spectra for various optical radiation effects on mammalian cells in vitro (cytotoxicity, pyrimidine dimer

formation, and transformation) indicate that some damage may occur at wavelengths up to, but not exceeding, 400 nm (ref. 6, 8, 9, 10).

(d) Activation of Viruses

No articles were found in the literature which indicate that blue light activates viruses. In addition, clinical experience with conventional bronchoscopy suggests that viral activation does not occur with the broadband white light source which includes a blue light component.

(e) Ocular Risks

A blue-light hazard analysis, performed by FDA, indicated that the ocular hazard for an accidental retinal exposure from the Xillix LIFE - Lung Fluorescence Endoscopy System is similar to that from the white light bronchoscope. Biological weighting functions implemented by the American Conference of Governmental Industrial Hygienists (ACGIH) to determine threshold limit values for exposure to light were used in the ocular hazard calculations of blue light from the subject device as compared to the standard white light source. These functions weight the ability of radiation at a specific wavelength to produce a given biological effect (e.g. photochemical injury).

Since the geometrical considerations for integrated radiance from the white light source and helium cadmium laser are similar due to use of the same fiber optics for both exams, therefore, the integrated radiance at the tip of the fiber optics for each type of examination differs by the effective radiant power of the two light sources. The effective weighted radiant power for the blue light wavelengths during a white light exposure was integrated from 405 nm to 500 nm using the radiant power data provided from the firm. Of course, the weighted radiant power for the He-Cd laser source was calculated for 442 nm. The effective blue-light weighted radiant power for the He-Cd laser source was calculated to be 30 mW while the same parameter was calculated to be 26 mW for the white light source; therefore, the ocular hazard is similar.

(f) Length of Procedures and Total Radiant Exposure

The fluorescence exam portion of the total bronchoscopic exam may last 75% longer than the conventional white-light portion of the exam. Taking into account this added exposure time, the biological effect will be proportional to the energy absorbed. For a single exam, while the radiant exposure from the laser may be

somewhat less than that from the white light, the combined radiant exposure at a specific tissue site for the combination exam may be significantly greater (35% to 70%) than that resulting from the white light source alone. No significant risk results from the use of the laser light source, however, since additional risk posed by increased time appears to be small as demonstrated by the scientific evidence which has been discussed in this section and by the lack of adverse effects in the clinical trials.

Radiation Safety Conclusion

The 442 nm laser radiation exposure from the Xillix LIFE - Lung Fluorescence Endoscopy System is less hazardous to the patient than conventional white light bronchoscopy. The combined examination with the Xillix LIFE - Lung Fluorescence Endoscopy System and conventional white light bronchoscopy results in a larger total dose. However, given that blue light at 442 nm is not mutagenic and is not associated with damage to DNA, this additional risk appears to be small as demonstrated by the lack of adverse effects in the clinical trials.

Electrical Stress Testing

Electrical Stress testing was performed on the Xillix LIFE - Lung Fluorescence Endoscopy System according to good laboratory practices. The tests were performed both by Xillix and in Europe by certified and authorized testing bodies. The testing, including extensive electrical safety testing, was performed by Laser-und Medecin Technologica Berlin GmbH to certify compliance with IEC 601-1 and for certification for the GS mark. Additional electrical safety and stress testing was performed by GMED to ensure French electrical safety for regulatory approval including IEC 601-1 and electromagnetic compatibility (EMC). The Xillix LIFE - Lung Fluorescence Endoscopy System also has undergone testing for EMC in compliance with CE-EMC regulations for sale in Europe. The performance of the device adheres to these standards.

Software Development and Testing

Software development for the Xillix LIFE - Lung Fluorescence Endoscopy System included requirements analysis, hazard analysis, design validation and software testing at unit subsystem and system acceptance test levels. The requirements analysis phase define the software specifications, which define the behavior of the software components.

Hazard analysis was initiated in the requirements analysis phase and continued throughout the development process. The results of the analysis were documented and used during

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the device design and device testing to anticipate and mitigate potential hazardous effects of component or subsystem failure. The hazard analysis identified three areas of concern, namely: loss of data, loss of program control and invalid data.

In situations of loss of program control or loss of data, the Xillix LIFE - Lung Fluorescence Endoscopy System cannot be used to indicate additional sites for biopsy or further study.

Data loss is usually associated with software or device failure. The Image software is designed to aid in the detection of device failure. Such conditions will be reported to the operator. In addition, a failed device will be disabled and not function. In extreme cases, the entire system may be shut down. Data loss caused by software malfunction is generally addressed by labeling and training. Operators will be trained to recognize a malfunctioning system and instructed on procedures to follow in the event of such failure.

Loss of program control also is associated with device failure, but may arise through operator error as well. If the loss of control is associated with hardware, an error is reported to the operator and the device will not function. Errors that may arise through the manufacturing process are addressed through procedural controls, i.e., good manufacturing practices (GMPs) and training, while those caused through maintenance activities are addressed through labeling and training.

Safeguards have been put into place to reduce the probability of the Xillix LIFE - Lung Fluorescence Endoscopy System presenting invalid data to the physician. Contradictory information due to invalid Xillix LIFE - Lung Fluorescence Endoscopy System data may cause some doubt in the physician's mind as to the presence or absence of suspicious tissue. This could lead to a delay in diagnosis or in the unnecessary biopsying of tissue. These additional safeguards have, therefore, been put in place to reduce the probability of such data failures:

a) Software diagnostics will detect equipment malfunctions that may lead to the display of invalid data. Such malfunctions will be reported to the operator, and any system functionality associated with the device will be disabled.

b) The operator verifies data entered into the system in order to reduce the occurrence of operator error.

c) Redundancy is built into the data stored on disk. This enables validity checks to be performed on data requested by the operator.

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IX. SUMMARY OF CLINICAL STUDIES

Study Objective

The study objective was to determine whether the Xillix LIFE - Lung Fluorescence Endoscopy System, when used as an adjunct to white light bronchoscopy (WLB), could improve the detection of moderate/severe dysplasia or carcinoma in-situ as compared to WLB alone. All tissue sites identified as bronchoscopically positive were biopsied for histopathologic evaluation. The biopsy results served as the "gold" standard for diagnosis.

Study Hypothesis

The Xillix LIFE - Lung Fluorescence Endoscopy System increases the detection rate by 50 % when used in conjunction with WLB, with each patient contributing no more than one histologically "positive" biopsy (i.e. moderate/severe dysplasia or worse).

The primary end point was to achieve at least a 50% increase in the detection rate of histologically positive lesions with the Xillix LIFE - Lung Fluorescence Endoscopy System, used in conjunction with WLB when compared to the sensitivity of WLB alone.

Inclusion Criteria

- Patients with known or suspected bronchogenic carcinoma who were scheduled for bronchoscopy as part of a standard diagnostic or staging workup.

  or

- Patients with Stage I completely resected lung cancer with no evidence of metastatic disease.

Exclusion Criteria

- patients with uncontrolled hypertension (systolic pressure > 200 mmHg, Diastolic pressure > 120 mmHg)
- patients with unstable angina
- patients with known pneumonia or suspected pneumonia

- patients with acute bronchitis within one month of the procedure
- patients with white count less than 2000 or greater than 20,000 and/or platelet count less than 50,000
- patients with known bleeding disorder
- patients who had received fluorescent photosensitizing drugs such as Photofrin within three months of the procedure
- patients with known reaction to topical xylocaine
- patients who were on, or had received chemopreventive drugs (e.g. retinoic acid) within 3 months of the procedure
- patients who had received ionizing radiation treatment to the chest within six months of the procedure
- patients who had received cytotoxic chemotherapy agents systematically within six months of the procedure
- patients who were pregnant
- patients previously enrolled in Part I of the study

Clinical Protocol Design

The study consisted of two separate parts. Both were conducted as multi center clinical trials. The Part I study is referred to as the "learning-curve" study and provided the investigators the experience of using the Xillix LIFE - Lung Fluorescence Endoscopy System. In addition, it confirmed that the Xillix LIFE - Lung Fluorescence Endoscopy System was at least as sensitive as white-light bronchoscopy in its ability to detect suspicious lung tissue. Part II was considered the pivotal study and is the basis for the effectiveness outcome data, while both Parts I and II contributed to the consideration of safety of the system. The protocol designs for Part I and Part II were exactly the same except that the number of the pathologists making the final biopsy diagnosis was one site pathologist for Part I, and one site plus two reference pathologists for Part II.

A complete WLB procedure was performed initially on the study patients, followed by a second complete bronchoscopy using the Xillix LIFE - Lung Fluorescence Endoscopy System. The entire procedure was videotaped and the suspicious lesions were classified under both WLB and the Xillix LIFE - Lung Fluorescence Endoscopy System, separately. After completing the Xillix LIFE - Lung Fluorescence Endoscopy System examination, the physicians were instructed to return to the white-light bronchoscopy to obtain matching tissue images to those identified as suspicious during the Xillix LIFE - Lung Fluorescence Endoscopy System examination. At the end of the examination, the suspicious lesions from both examinations were biopsied. One to four normal areas were also biopsied in order to assess the ability of the Xillix LIFE - Lung Fluorescence Endoscopy System to accurately diagnose normal mucosa. The visual diagnosis using WLB and the Xillix LIFE - Lung Fluorescence Endoscopy System were compared to the final histopathological biopsy diagnosis and the sensitivity, specificity, PPV (Positive Predictive Value) and NPV (Negative Predictive Value) were calculated.

Bronchoscopic Classifications

The color mix displayed on the image monitor during fluorescence examinations is a combination of the red and green components of the autofluorescence. The color mix for tissue varies due to differences in the autofluorescence emissions of various types of bronchial tissue (Figure 1). These differences may then be related to standard bronchoscopic tissue classifications. The bronchoscopic appearance of the tissue was classified into the following categories for the WLB exam and the exam utilizing the Xillix LIFE-Lung Fluorescence Endoscopy system (WLB+fluorescence):

Class I "Normal": No visual abnormalities

Class II "Abnormal": Inflammation, trauma, anatomical abnormalities, metaplasia and mild dysplasia

Class III "Suspicious": Suggestive of moderate to severe dysplasia, CIS, or invasive carcinoma

The color mix of displayed images varies based on the level of abnormality and anatomical characteristics. Class I (bronchoscopically negative) tissue typically appears green. Class II (bronchoscopically negative) tissue varies in appearance from diffuse low level reddish-brown to characteristically shaped anatomical abnormalities. Class III (bronchoscopically positive) lesions typically appear as focal or delineated reddish-brown. The Clinical Information and Training Manual provides detailed information concerning the variety of images produced during fluorescence examinations.

Pathologic Ratings

Histopathologic rating was standardized in nine major codes from 1.0 to 9.0 and subclassified 0.1 to 0.5. Code 9.0 denotes an unsatisfactory biopsy (various reasons).

Histopathological Codes (Primary)

1.0	Normal	6.0	Carcinoma In Situ (CIS)
2.0	Inflammation	7.0	Micro invasive
3.0	Hyperplasia	8.0	Carcinoma
4.0	Mild Atypia (Dysplasia)	9.0	Unsatisfactory
5.0	Moderate/Severe Atypia (Dysplasia)		

Physicians were required to take biopsies of all Class III areas discovered by white light and/or fluorescence examination for pathologic examination. The physician was also required to take one random biopsy from a site classified as Class II by white light and/or fluorescence examination, regardless of the number of Class II areas located. In addition patients who had Class III biopsies evaluated were required to have a minimum of at least one random biopsy taken from a Class I area (visually normal under white light and fluorescence exams). For patients in whom no Class III areas were found during either white light or Xillix LIFE - Lung Fluorescence Endoscopy System examinations, physicians took 1- 4 random biopsies.

For the pivotal clinical trial, histopathologic rating was performed by the site pathologist and the two reference pathologists, independently. The final rating was determined by majority rule, unless no majority existed. An example of when no majority decision was reached is as follows: one pathologist would rate the biopsy sample as 4 - mild dysplasia, one would rate it as 5 - moderate dysplasia, and the third would rate it as 9 - unsatisfactory sample. In those cases where there was not an initial majority decision, a rating decision was then reached in one of two ways. First, one reference pathologist was permitted to review the three original ratings. If that reference pathologist, after re-examining the tissue, was able to agree with one of the other ratings, then a majority was reached. However, if that pathologist was unable to agree with one of the other ratings, then the second reference pathologist reviewed the three decisions and was to determine if he/she could agree with one of the other ratings. If a majority decision could not be reached in this manner, then the two reference pathologists discussed the ratings and jointly came to a consensus. All ratings were made blinded to all bronchoscopic classifications of tissue.

Sample Size

The study was designed to demonstrate that the WLB plus the Xillix LIFE - Lung Fluorescence Endoscopy System (WLB + fluorescence) improved the detection of patients with histologically positive bronchial abnormalities as compared to WLB alone. It was determined that the evaluation of 250 patients would be necessary in order to demonstrate that the WLB + fluorescence yielded 50% more histologically positive lesions than WLB alone, with a power of 90% or greater.

However, the study was terminated after 864 biopsies were taken from a total of 173 patients. These patients yielded a total of 142 "positive" lesions as determined by histologic examination. WLB alone detected 35 histologically positive lesions, and WLB + fluorescence detected 95 histologically positive lesions. Originally, the applicant performed statistical analysis on the number of "positive" lesions detected rather than on the number of "positive patients" that were detected (as originally planned). Since the detection rate of the WLB + fluorescence was greater than the 50% criteria established as the initial outcome criteria, the applicant determined that the study could be terminated at 173 patients (based on the strength of the number of "positive" lesions correctly identified). (NOTE: actual clinical trial outcome resulted in an average of 2 histologically "positive" -- moderate/severe dysplasia or worse -- lesions per patient when evaluated with WLB and the Xillix LIFE - Lung Fluorescence Endoscopy System, not one as originally anticipated).

Subsequently, the applicant also analyzed the data based on the number of "positive patients" detected since the original outcome determination was based on "positive patients" identified and not the number of "positive" lesions that were identified. Out of the 173 patients enrolled in the study at the time the study was terminated, there were 75 patients who had been identified with moderate/severe dysplasia or worse. WLB alone detected 28 patients and the WLB + fluorescence examination detected 56 patients.

Institutions and Investigators

There were seven investigational institutions included in the clinical trial, including the British Columbia Cancer Agency in Vancouver, Canada, and six U.S. institutions.

The two designated reference pathologists were Dr. Adi Gazdar, Simmons Cancer Center, Univ. of Texas Southwestern at Dallas, and Dr. Jean LeRiche, British Columbia Cancer Agency, Vancouver, Canada.

X. ANALYSIS OF DATA

The device was studied in a two-phase multi center trial divided into Part I and Part II. The Part I study was referred to as the learning curve study and provided investigators with the experience of using the device. Part I included a total of 146 patients enrolled resulting in 751 biopsies of which 675 were evaluable. Part II included a total of 173 patients resulting in 864 biopsies of which 700 were evaluable. Part II was considered the pivotal study and was the basis for the effectiveness outcome data, while both Parts I and II and additional data from three phase II clinical trials contributed to the consideration of the safety of the device.

Patient Demographics

- Most of the patients in the study group were smokers (>90%).
- Study enrollment included 378 men (67%) and 173 women (33%).
- Age of the study subjects ranged from 36 to 87 years with a mean age of 62 years.
- Patients were not stratified by race.

Safety (including adverse events which occurred during clinical use of the device)

Clinical safety of the Xillix LIFE - Lung Fluorescence Endoscopy System was assessed by reviewing the adverse events which occurred during Part I and Part II of the clinical trial, plus an earlier study conducted at the British Colombia Cancer Agency (BCCA). There was a total of 319 patients who participated in either Part I (146 patients) or Part II (173 patients) of the study described above. There were 223 patients in the BCCA study. The total of 551 patients were considered in this clinical safety section, with the adverse events as follows:

(a) one incident of post-bronchoscopy bronchitis (BCCA study)

(b) one incident of hypoxemia, less than 50 % oxygen saturation (Part I of clinical trial)

(c) one incident of drug reaction to topical cocaine which was used to control excessive bleeding from a biopsy site in a 76-year-old female (Part II of clinical trial).

All three incidents were considered to have been caused by bronchoscopic procedures, not specifically related to the Xillix LIFE - Lung Fluorescence Endoscopy System device. The rate of adverse events for the WLB + fluorescence is calculated as less than 0.5%, similar to WLB alone.

An additional safety concern associated with the use of the Xillix device is the percentage of biopsies taken from sites not originally targetted for biopsy during the examinations. In Part II of the clinical trial, this rate was calculated as 1% (11 of 864 biopsies).

Effectiveness

Multi-Center Trial - Part I

For analysis, lesions classified as Class I and II by bronchoscopy examination were collapsed into the "negative" (-) group and the lesions classified as Class III were placed in the "positive" group "+" (suggestive of moderate/severe dysplasia or worse). As noted above, 675 of the biopsies could be evaluated by the pathologist. Of these, 53 lesions were found to be histologically "positive" (moderate/severe dysplasia, CIS, or invasive carcinoma) on biopsy examination (biopsy examination was considered the "gold" standard to determine the final diagnosis).

Using WLB alone, 30 of 53 lesions were classified correctly by the physician as "+". When utilizing the combined modalities, WLB plus the Xillix LIFE - Lung Fluorescence Endoscopy System (WLB + fluorescence), 41 bronchoscopically positive lesions were determined to be moderate/severe dysplasia or worse by histologic evaluation.

The data from the "learning-curve" study indicated that the sensitivity of the WLB + fluorescence was increased over the sensitivity of the WLB alone. The negative predictive value (NPV) of the WLB + fluorescence examination was no different from that of WLB alone.

The study demonstrated the learning effect in the ability to correctly identify "positive" lesions that is gained from experience with the device. As Part I of the study progressed,

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the physicians became more proficient at reading the images produced from the bronchial tissue autofluorescence elicited by the Xillix LIFE - Lung Fluorescence Endoscopy System laser.

Multi-Center Trial - Part II - Pivitol Study

The study design and endpoints were the same as in Part I, except that the final biopsy diagnosis was made by three pathologists; one site and two reference pathologists. A total of 864 biopsies on 173 patients were performed. Out of these 864 biopsies, 164 were excluded (reasons included not having adequate tissue samples). This left 700 evaluable lesions.

Of the 164 excluded biopsy specimens there was approximately a 70% disagreement between the diagnosis made by the site pathologist and the two reference pathologists. This raised a serious concern as to whether or not the remaining data from 700 biopsies could be biased.

Evaluation of the discrepancies revealed the following: the site pathologist sometimes read biopsies that contained no tumor cells in a routine manner and simply called the biopsy "normal", rather than using the classification system established in the protocol. Reference pathologists read the biopsy specimens strictly according to the code and classification system developed for the clinical trial. Therefore, some biopsy specimens that were called "normal" by the site pathologist, because there were no tumor cells, were coded as 'unsatisfactory' by the reference pathologists when there was not enough tissue for a biopsy rating. It was concluded that the reference pathologists reading used the appropriate methodology.

Demographics

- Most of the patients in the Part II study group were smokers (93%). American Cancer Society (ACS) data shows smoking is responsible for 90% of all lung cancers
- Study enrollment included 108 men (62%) and 65 women (38%)
- The study subjects ranged in age from 36 years to 87 years with a mean age of 62.8 years. One hundred ten patients (64%) were 60 years of age or older. These numbers are consistent with lung cancer prevalence data from ACS. There was no indication that the device was any more or less effective in any age group

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- Patients in this study were not stratified by race. Figures from ACS do not show a statistically significant disease prevalence difference according to race. Based upon the device technology, there is no reason to anticipate that racial makeup would influence the safety or effectiveness of the Xillix system

Lesion-Based Data Analysis

As in Part I of the study, the three bronchoscopic image classifications were collapsed into two groups; " + " and " - " . Of the 700 evaluable lesions assessed in the clinical study of the Xillix system, 142 (20.3%) of these lesions were rated as histologically "positive," i.e., the biopsy rated as moderate/severe dysplasia, CIS, or invasive carcinoma. Results of the comparison of the physician's identification of "positive" lesions by WLB + fluorescence examination and by WLB alone to the final histopathological results of the 700 evaluable biopsies are presented in the following tables.

Lesion Based Biopsies

	+	-
WLB (+)	35	54
WLB (-)	107	504
Total	142	558

Biopsy Results

	+	-
WLB plus Fluorescence (+)	95	190
WLB plus Fluorescence (-)	47	368
Total	142	558

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Summary of the data (based on 700 biopsy lesions)

	WLB	WLB + Fluorescence
Sensitivity	0.25	0.67
Specificity	0.90	0.66
Positive Predictive Value (PPV)	0.39	0.33
Negative Predictive Value (NPV)	0.83	0.89
False Positive rate	0.10	0.34

Further analysis of the data for two subgroups:

a) Patients with known lung cancer:

	WLB	WLB + Fluorescence
Sensitivity	0.53 (8/15)	0.73 (11/15)

b) Patients with suspected lung cancer:

	WLB	WLB + Fluorescence
Sensitivity	0.21 (27/127)	0.66 (84/127)

These data show differences between the positive predictive value of the WLB + fluorescence examination and use of the WLB alone. The positive predictive value of WLB alone was estimated by the proportion of lesions classified as class III (bronchoscopically positive) under WLB examination that were also determined to be histologically positive. The positive predictive value of WLB + fluorescence was estimated by the proportion of lesions determined to be bronchoscopically positive under WLB + fluorescence examination that were also determined to be histologically positive by analysis of biopsies.

The specificity of the WLB + fluorescence examination is reduced as compared to that of the WLB alone. This decrease is due to the tripling of the false positive rate found with the WLB + fluorescence examination compared to the use of WLB alone.

The fluorescence examination resulted in an additional 196 biopsies being taken, which yielded an additional 60 "positive" biopsies.

The addition of the fluorescence examination resulted in an increase in the negative predictive value. The negative predictive value of WLB alone was estimated by the proportion of lesions classified as "negative" under WLB examination that were also determined to be "negative" at histopathological review. The negative predictive value of WLB + fluorescence was estimated by the proportion of lesions classified as "negative" under WLB + fluorescence examination that were also determined to be "negative" at histopathological review.

Although this lesion based data showed an improvement of the sensitivity of the Xillix LIFE - Lung system plus the WLB over the WLB when used alone, in its ability to detect an increased number of lesions in the moderate/severe dysplasia or worse categories, it does not reflect the sensitivity of the Xillix LIFE - Lung system in detecting the number of patients who were identified as being "positive" for suspicious bronchial tissue.

Patient-Based Data Analysis

The patient based data were categorized in a similar manner as was the lesion based data. Therefore, the following analyses were made: WLB alone, WLB + fluorescence, and biopsy results. A patient was considered bronchoscopically "positive" for an examination type (WLB or WLB+fluorescence) when at least one lesion was Class III. A patient was considered bronchoscopically "negative", when all examinations yielded either a Class I or II determination. Patients were histologically positive if final histopathological rating was moderate/severe dysplasia or worse for one or more lesions. This analysis is presented in the following tables.

Patient Results (173 total)

	+	-
WLB (+)	28	22
WLB (-)	47	76
Total	75	98

By Patient Biopsy Results (173 total)

	+	-
WLB + Fluorescence (+)	56	57
WLB + Fluorescence (-)	19	41
Total	75 +	98 = 173

Data Summary Table (based on 173 patients)

	WLB	**WLB + Fluorescence**
Sensitivity	0.37	0.75
Specificity	0.78	0.42
Positive Predictive Value (PPV)	0.56	0.50
Negative Predictive Value (NPV)	0.62	0.68
False positive rate	0.22	0.58

Further analysis of the data for two subgroups:

a) Patients with known lung cancer:

	WLB	WLB + Fluorescence
Sensitivity	1.00 (6/6)	1.00 (6/6)

b) Patients with suspected lung cancer:

	WLB	WLB + Fluorescence
Sensitivity	0.32 (22/69)	0.72 (50/69)

The patient-based sensitivity data demonstrated that the improvement in detection using the WLB + fluorescence over the use of WLB alone (an improvement from 0.37 for WLB to 0.75 for WLB + fluorescence), and was large enough to reject the null hypothesis.

The specificity is significantly decreased from 0.78 for the WLB examination to 0.42 for the WLB + fluorescence examination. This drop in specificity for the WLB + fluorescence examination is due to the increase in the number of false positives in the WLB +

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fluorescence examination, when compared to the WLB alone examination (as was also noted in the analysis of the lesion data, presented earlier).

These results indicate that while the false positive rate increased with the addition of the fluoresence examination resulting in additional biopsies, the sensitivity also increased. However, 19 patients classified as "negative" by WLB + fluorescence were actually determined to be "positive" by histopathology (false negatives). Therefore, one cannot assume the absence of disease despite a "negative" classification following a WLB + fluorescence examination.

Gender-based Analysis

Sensitivity of the Xillix system in males was 0.68 and in females was 0.64. There was no statistically significant difference between the gender-based cohorts indicating that the device was equally effective for both gender groups.

Reproducibility Analysis

To test reproducibility for fluorescence examinations, the applicant submitted an abbreviated, retrospective reproducibility study. The two sites which contributed the largest number of patients to the pivotal clinical trial participated. The applicant randomly selected images within each classification totaling 25 cases per institution. The images were chosen only from the digital images which were stored in the computer during the clinical trial (videotaped images were not used). The selected digital images consisting of approximately the same number of cases between the classes; I, II and III (slightly larger number of class II), were sent to the other institution without labeling the original bronchoscopic results. The "receiving" institution reviewed the still images from the Xillix LIFE - Lung Fluorescence Endoscopy System and sent back its readings to the applicant's monitoring panel. The results were analyzed by calculating the percentage of matching classifications between the original physician and the physician at the second institution.

There were 48 images reviewed in this study (2 images of the 50 cases in this reproducibility analysis were not reviewed because one institution deemed two of the images as unrecoverable from the file).

There were 27 exact matches (56%) between the 2 institutions. When Class I and Class II image readings were both considered bronchoscopically negative and Class III readings to be bronchoscopically positive, the reproducibility was found to be 71%.

Assessment of this limited data revealed:

a) A 31% agreement calculated for images in Class I

b) Approximately 50% agreement calculated for images in Class II

c) An 80% agreement calculated for images in Class III

d) that when there was a question between Class II and III, the most common histologic outcome was benign (90%)

A post-market study is required to further investigate the reproducibility for classification of fluorescence images. This will permit a larger number of images to be compared between practitioners and allow for use of the videotaped images as well.

Analysis of Normal Tissue-Biopsy Data

A total of 243 biopsies were obtained from tissue tabulated as Class I by both the WLB examination and the combined WLB plus Xillix LIFE - Lung Fluorescence Endoscopy System examinations. A tabulation and overview of the histological results from these 243 biopsies follows:

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Pathology Results	Description	Number. of Normal Biopsy	% of Total Evaluable Normal (210)
Codes 1.0 -2.5	Normal, Inflammation	39	18.6%
Codes 3.1 - 4.2	Hyperplasia/Metaplasia, mild Dysplasia	150	71.4%
Codes 5.1 - 8.5	Moderate/Severe Dysplasia, or worse	21	10 %
Excluded	Inevaluable, No Majority Pathology	33	
Total Normal 'Biopsy'		243	

A total of 210 biopsies were evaluable. The above table shows that 18.6% of the biopsies determined to be Class I by the physicians' examination of the bronchoscopic images were actually rated as normal/inflamed during the tissue-pathology evaluations. The majority of histology (71.4%), although histologically negative for moderate/severe dysplasia or worse, were determined to be abnormal (i.e. mild dysplasia or hyperplasia/metaplasia).

The ability of the Xillix LIFE - Lung Fluorescence Endoscopy System plus WLB examinations to correctly classify histologically negative tissue as class I or class II i.e. Negative Predictive Value (NPV), was 90% (18.6% + 71.4%). Therefore, pathology results showed that 10% of the normal appearing images actually represented moderate/severe dysplasia, CIS, or invasive carcinoma (i.e. false negative rate).

Risk/Benefit Assessment

Some degree of increased patient risk can be expected due to the prolonged bronchoscopic time required by the addition of the Xillix LIFE - Lung Fluorescence Endoscopy System to the WLB examination (additional time ranging from 5 to 40 minutes) and by a significant increase (from 89 to 285) in the number of biopsies obtained. However, the adverse events which occurred during three clinical safety studies conducted with the Xillix system were not directly attributed to the Xillix system and were of minimal clinical significance.

This increased risk is balanced by the increase of sensitivity found with the use of the Xillix LIFE - Lung Fluorescence Endoscopy System plus WLB (75%) as compared to WLB alone (37%) in detecting patients with abnormal bronchial tissue consisting of moderate/severe dysplasia, CIS, or invasive carcinoma.

XI. CONCLUSIONS FROM CLINICAL STUDIES

The clinical investigations conducted with the Xillix LIFE-Lung Fluorescence Endoscopy System, used as an adjunct to white light bronchoscopy, showed that the Xillix device plus white light bronchoscopy can enhance the physician's ability, versus white light alone, to identify and locate bronchial tissue suspicious for moderate/severe dysplasia or worse, for biopsy and histologic evaluation in appropriate patient populations. This device has been demonstrated safe and effective when used as indicated.

XII. PANEL RECOMMENDATIONS

At a public meeting on June 11, 1996, the Ear, Nose and Throat Devices Panel unanimously recommended approval of the PMA, subject to the following conditions:

1. Revised labeling which accurately reflects data submitted in the PMA.
2. Submission of a protocol and agreement to conduct a postmarket study to support reproducibility of the data obtained by the device.

The recommendation of the voting members of the ENT Devices Panel concerning training on the use of the Xillix LIFE - Lung Fluorescence Endoscopy System was that appropriate training should be "strongly recommended". The majority of the panel members did not believe there should be a mandatory training requirement. The panel indicated that physicians who will be using the device should be adequately trained and that certain criteria be established to ensure consistency in the training program.

XIII. CENTER FOR DEVICES AND RADIOLOGICAL HEALTH (CDRH) DECISION

CDRH agreed with the panel's recommendation that labeling revisions were required and that a postmarket study to evaluate reproducibility of the data obtained by the device should be conducted. In addition, CDRH requires that the use of the device be restricted to physicians who have completed appropriate training in flexible fiber optic bronchoscopy and who have received training in the use of the Xillix LIFE - Lung Fluorescence Endoscopy System.

CDRH requires that a postmarket reproducibility study, utilizing the dynamic video images which the physicians utilizes in determining image classification, be conducted to augment the reproducibility data submitted as part of the PMA which was collected using only "still" digital images stored in the system's computer. The post approval study will provide a larger data base for assessing reproducibility of image classification utilizing the fluorescence endoscopy system.

CDRH requires that the provision for training be mandatory. This is based upon the understanding that there was a learning curve effect demonstrated by the investigators in the clinical trial. The clinical trial that supported the safety and effectiveness of the Xillix LIFE - Lung Fluorescence Endoscopy System did not begin until each investigator had demonstrated a pre-determined level of competency with the device.

CDRH requires that the company provide a total training package and update the training program over time. As part of the package, the firm will conduct hands-on training at the time of a system installation. Training instructors will review all of the topics contained in the Training Manual plus other materials that may be given out by the firm. Training will be comprehensive in scope and will provide an understanding of the overall Xillix LIFE - Lung Fluorescence Endoscopy System and an understanding of all functional system components.

CDRH also requires the company to maintain an ongoing, complete training program for successive health care professionals who wish to use the Xillix LIFE - Lung Fluorescence Endoscopy System, but who were not present at the time of a system installation. In this regard, the firm will determine whether to return to a specific site to give a training course, whether to have designated locations where training can be given or whether to have the training taught by a practitioner who completed the company's training program and who demonstrated scientific and clinical competence in the use of the device.

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Furthermore, CDRH added another condition of approval related to device calibration. The applicant was required to submit a protocol for long term equipment calibration which will take place at the site where the device is in use.

XIV. APPROVAL SPECIFICATIONS

Directions for use: See the labeling.

Hazards to Health from Use of the Device: See Indications, Contraindications, Warnings, precautions and Adverse Events in the labeling.

Conditions of Approval: CDRH's approval of this PMA is subject to full compliance with the conditions described in the approval order.

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References

1. Cordasco, EM Jr., et. al. Bronchoscopically Induced Bleeding. A Summary of Nine Years Cleveland Clinic Experience and Review of the Literature. Chest 1992: 102(4); 1310-
2. Lamola, AA, et.al., Fluorometric Study of the Partition of Bilirubin Among Blood Components: Basis for Rapid Microassays of Bilirubin and Bilirubin Binding Capacity in Whole Blood. Analyst Biochm 100:25-42 (1979).
3. Galland, P; Senger, H. Flavins as Possible Blue-Light Photoreceptors: Photoreceptor Evolution and Function, Holmes MG, ed., Academic Press, Toronto, pp. 65-124.
4. Coohill, T.P. Action Spectra for Mammalian Cells in vitro, pp 1 - 37.
5. Song, P.S., et. al. Properties and Evolution of Photoreceptors. Photoreceptor Evolution and Function, Holmes, M.G., ed., Academic Press, Toronto, pp. 21-63 (1991).
6. Anderson, R.R; Parish, J.A. Optical Properties of Human Skin. The Science of Photomedicine; Pregan and Parrish, eds.; Plenum Press, New York, pp: 147-194 (1982).
7. McDonagh, A.F. Light Effects on Transport and Excretion of Bilirubin in Newborns. In: The Medical and Biological Effects of Light, Wurtman, R.J., et.al. editors. New York Academy of Sciences, pp. 65 - 72 (1985).
8. Sutherland, B.M., et. al. Photoreactivation and Other Ultraviolet Visible Light Effects on DNA in Human Skin. The Medical and Biological Effects of Light; Wurtman, et. al.,eds.; New York Academy of Sciences, pp. 73-79 (1984).
9. Sutherland, B.M., et. al. DNA Photoreactivating Enzyme From Placental Mammals; Origin and Characteristics: Biochem 13: 4710-4715 (1994).
10. Thompson, K.P., et. al. Therapeutic and Diagnostic Application of Lasers in Ophthalmology: Proc IEEE 80(6): 838-59 (1992).
11. Sliney, D., Wolbarsht, M. Safety With Laser and Other Optical Sources: New York, Plenum Publishing Co. (1980).
12. Mainster, M.A. Finding Your Way in the Photoforest. Laser Effects for Clinicians: Ophthalmology 91 (7): 886-88 (1984).

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PACKAGE INSERT

DEVICE DESCRIPTION

The Xillix LIFE-Lung Fluorescence Endoscopy System uses a narrow band Helium-Cadmium laser, attached to an Olympus BF-20D bronchoscope in order to transmit visible light (442 nm) into bronchial tissue. The light elicits a fluorescence response (autofluorescence) from the tissue which is received by the bronchoscope, filtered, and displayed as either a real time image or a still digital image on a monitor. *No drugs are used to enhance the fluorescence emissions.*

INDICATIONS FOR USE

The Xillix LIFE-Lung Fluorescence Endoscopy System is indicated for use as an adjunct to white light bronchoscopy (WLB), using an Olympus BF-20D bronchoscope, to enhance the physician's ability to identify and locate bronchial tissue, suspicious for moderate/severe dysplasia or worse, for biopsy and histologic evaluation in the following patient populations :

1. Patients with known or previously diagnosed lung cancer; and

2. Patients with suspected lung cancer including (a) patients with Stage I completely resected lung cancer, with no evidence of metastatic disease, who are at risk for secondary disease, and (b) patients suspected of having lung cancer because of clinical symptoms such as positive sputum cytology, hemoptysis, unresolved pneumonia, persistent cough, or positive X-ray.

CONTRAINDICATIONS

The Xillix LIFE-Lung Fluorescence Endoscopy System should not be used on the following patients:

1. Patients who are contraindicated for white light bronchoscopic examination including:

- patients with uncontrolled hypertension (systolic pressure > 200 mmHg, diastolic pressure > 120 mmHg)
- patients with unstable angina
- patients with white blood count less than 2000 or greater than 20,000, and/or platelet count less than 50,000
- patients with known bleeding disorder or patients on anticoagulant therapy.

2. Patients who are contraindicated for fluorescence examination including:

- patients who have received fluorescent photosensitizing agents (hematoporphoryn derivatives) within three months prior to the procedure
- patients who are on, or have received chemopreventive drugs (e.g. retinoic acid) within 3 months prior to the procedure
- patients who have received ionizing radiation treatment to the chest within six months prior to the procedure
- patients who have received cytotoxic chemotherapy agents systematically within six months prior to the procedure.

WARNINGS

1. The Xillix LIFE- Lung Fluorescence Endoscopy System is not indicated for use as a stand alone diagnostic device and should not be used as such. The Xillix LIFE-Lung Fluorescence Endoscopy System must be used in conjunction with the Olympus BF-20D flexible fiber optic bronchoscope.

2. The physician should perform a complete white light bronchoscopy, then repeat the examination using fluorescence. Because blood may mask the autofluorescence image, the physician should perform the biopsy procedure, moving from distal to proximal, only after completing both examinations. All lesions categorized as Class III should be biopsied, whether they were found under white light bronchoscopy, fluorescence, or both.

3. The Xillix LIFE-Lung Florescence Endoscopy System is intended to identify and locate abnormal bronchial tissue for biopsy. All diagnoses are determined by histological review.

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5. Safety and effectiveness in pregnant women have not been established.

6. The presence of acute pulmonary infection including bronchitis and pneumonia may increase the risks associated with bronchoscopy and the risk of obtaining false positive readings from this examination.

ADVERSE EVENTS

The following adverse events were reported during the clinical evaluation of this device:

1. one incident of post-bronchoscopy bronchitis
2. one incident of hypoxemia, less than 50 % Oxygen saturation
3. one incident of drug reaction to topical cocaine which was used to control excessive bleeding from a biopsy site in a 76 year old female.

Issues pertaining to potential adverse events are summarized as follows:

Patients who are indicated for use of this device are those already indicated for standard fiberoptic examination for known or suspected lung cancer. Additional biopsies may be taken as a result of the fluorescence examination. The length of the bronchoscopic examination will be longer for the combined examinations than it is for white light bronchoscopy alone.

Potential adverse events of the Xillix LIFE-Lung Fluorescence Endoscopy System, while similar to those of white light bronchoscopy, may be potentiated by the increased number of biopsies and increased examination time associated with use of the device. These may include the following:

- infection
- bleeding
- pneumothorax (lung collapse)
- hypoventilation (inadequate breathing ocaasionally requiring use of a mechanical ventilator)
- reaction to medications (including local and intravenous anesthetics, medications used to control biopsy site bleeding, anti-arrythmics, etc.)
- arrythmias (irregular heart beat),
- hypotension (low blood pressure)
- postoperative soreness of the throat and/or bloody sputum
- and death

4. The Xillix LIFE-Lung Fluorescence Endoscopy System should not be used in conjunction with photosensitizing agents.

5. Patients on anticoagulant therapy should discontinue use prior to examination for the period of time specified by their physician.

6. Patients with known sensitivity to local anesthetic agents should be carefully assessed prior to being considered for this examination.

7. Physicians who have red/green color blindness should not attempt to use the Xillix device, because they will not be able to judge the gradations of color associated with normal and abnormal bronchial tissue.

PRECAUTIONS FOR USE

1. The Xillix LIFE - Lung Fluorescence Endoscopy System is restricted by Federal Law to be used only by physicians who have completed appropriate training in flexible fiber optic bronchoscopy and who have been trained in the use of the Xillix device.The physician should use his/her judgment and experience in interpreting the fluorescence images. For further information refer to Xillix LIFE-Lung Fluorescence Endoscopy System Clinical Information and Training Manual.

2. The Xillix LIFE-Lung Fluorescence Endoscopy System may show fluorescence images that could be incorrectly interpreted by the physician. Images that appear bronchoscopically positive may be caused by inflammation, scope or suction trauma, scar tissue, presence of photosensitizing agents, or chemopreventive agents. Images that appear bronchoscopically negative may not always accurately indicate the absence of abnormal tissue, i.e. not all abnormal bronchial tissue will be detected.

3. The physician may perform the biopsies in white light or fluorescence. For lesions less than 5 mm in diameter which are not visible under white light bronchoscopy, the physician should perform the biopsy under fluorescence mode.

4. The Xillix LIFE - Lung Fluorescence Endoscopy System provides a mechanism to store, label and retrieve a digital image, in fluorescence and white light, of the suspicious area. The stored images, site-labeling and the physician's observational skills help to ensure that the biopsy is taken from the correct site as with WLB. Since there is a small chance of error, i.e. biopsy taken from an incorrect site, caution should be exercised when relying on these stored images to target the biopsy. An error could lead to misdiagnosis of a patient if normal tissue is inadvertently biopsied instead of the targetted abnormal tissue.

See also the Clinical Safety section which appears under "Results of Clinical Trial". This section provides further analysis of the adverse effects which occurred during clinical studies which evaluated the use of the Xillix LIFE-Lung Fluorescence Endoscopy System

INSTRUCTIONS FOR USE

The color mix displayed on the image monitor is a combination of the red and green components of the autofluorescence. The color mix for tissue varies due to differences in the autofluorescence emissions of various types of bronchial tissue. These differences may then be related to standard bronchoscopic tissue classifications using as a scale such as:

Class I "Normal": No visual abnormalities

Class II "Abnormal": Inflammation, trauma, anatomical abnormalities, metaplasia and mild dysplasia

Class III "Suspicious": Suggestive of moderate to severe dysplasia, carcinoma-in-situ, or invasive carcinoma

The color mix of displayed images varies based on levels of abnormality and anatomical characteristics. Class I (bronchoscopically negative) tissue typically appears green. Class II (bronchoscopically negative) tissue varies in appearance from diffuse low level reddish-brown to characteristically shaped anatomical abnormalities. Class III (bronchoscopically positive) lesions typically appear as focal or delineated reddish brown.

Detailed instructions for use for the Xillix LIFE-Lung Fluorescence Endoscopy System are contained in the Operator's Manual. In addition, please refer to the Clinical Information and Training Manual for additional information concerning the use of the device and the images it produces.

CAUTION: Federal Law restricts this device to sale, distribution and use by or on the order of physicians who have completed appropriate training in flexible fiber-optic bronchoscopy and who have been trained in the use of the Xillix device.

INTERPRETATION OF RESULTS

The interpretation of the images is dependent upon physician training and experience. As part of the required training in the use of the device, physicians receive copies of the Clinical Information and Training Manual. This manual describes the guideline for interpretation of white light and fluorescence images. (For detailed information see "Appearance of Pathological Conditions and Guidelines for Interpretation of White Light and Florescence Images," Clinical Information & Training Manual).

CLINICAL TRIAL

This device was studied in two multicenter clinical trials identified as: Part I and Part II. The Part I study was referred to as the "learning-curve" study and provided the investigators the experience of using the Xillix LIFE-Lung Fluorescence Endoscopy System. Part II was considered the "pivotal study" and was the basis for the effectiveness outcome data, while both Parts I and II and additional data from three phase II clinical trials contributed to the consideration of safety of the device.

Demographics

- Most of the patients in the study group were smokers (>90%).
- Study enrollment included 378 men (67%) and 173 women (33%).
- The study subjects ranged in age from 36 years to 87 years with a mean age of 62 years.
- Patients in this study were not stratified by race.

Safety

Clinical safety of the Xillix LIFE - Lung Fluorescence Endoscopy System was assessed by reviewing the adverse events which occurred during Part I and Part II of the clinical trial, plus a pre- Part I study conducted at the British Colombia Cancer Agency (BCCA). There was a total of 319 patients who participated in Part I (146 patients) and Part II (173 patients). There were 223 patients in the BCCA study. The total of 551 patients and 2115 biopsies are considered in this clinical safety analysis, with three reported significant adverse events as follows:

1. one incident of post-bronchoscopy bronchitis (BCCA study)

2. one incident of hypoxemia , less than 50 % Oxygen saturation (Part I of clinical trial)

3. one incident of drug reaction to topical cocaine which was used to control excessive bleeding from a biopsy site in a 76 year old female (Part II of clinical trial).

None of the three reported incidents were considered to have been directly related to the Xillix device. The rate of adverse events for the Xillix device plus WLB is calculated as less than 0.5%, which did not differ from that during use of WLB alone.

An additional safety concern associated with use of the Xillix device, although not strictly speaking an adverse event, is the percentage of biopsies taken from sites other than those which had initially been targetted for biopsy. In Part II of the clinical trial, this rate was calculated as 1% (11 of 864 biopsies).

Study Design of Part II of Clinical Trial:

A total of 173 patients generating 700 evaluable biopsies were examined at seven institutions.

The 173 patients enrolled in the study first underwent a complete white light bronchoscopic examination of the tracheobronchial tree (to the IV generation bronchi) using the Olympus BF - 20D bronchoscope. During the procedure the physician identified the location of suspicious tissue according to a standard three point scale:

Class I "Normal": No visual abnormalities

Class II "Abnormal": Inflammation, trauma, anatomical abnormalities, metaplasia or mild dysplasia

Class III "Suspicious": Suggestive of moderate to severe dysplasia, CIS, or invasive carcinoma

While the bronchoscope was still in place the physician switched to the Xillix LIFE-Lung Fluorescence Endoscopy System and repeated the entire examination. At the end of the examination the physician was required to take biopsies of all Class III areas and a minimum of one random normal (Class I) area. If the physician did not

identify any areas of Class III, they were required to take two random normal (Class I) areas. Biopsies were reviewed by a pathologist at the clinical trial site, and then sent to two reference pathologists for review blinded to the image classification. The histologic diagnosis was determined using a 9 point scale, as outlined in the Clinical Information & Training Manual. The final pathological diagnosis was determined typically by the majority decision of the three pathologists. However, in cases where no majority existed the final rating was achieved by re-review by a reference pathologist or consensus of the reference pathologists.

Effectiveness

Effectiveness was assessed by comparing the accuracy of white light bonchoscopy alone (WLB) with the accuracy of white light bronchoscopy plus the Xillix LIFE-Lung Fluoresence Endoscopy System (WLB + fluoresence) in identifying lesions which require biopsy for histological evaluation. Both methods were compared to histology (the gold standard) in terms of their ability to locate cancerous and precancerous lesions (moderate/severe dysplasia or worse).

Effectiveness data is presented in two ways:

-- the number of **patients** in whom at least one lesion was accurately identified (bronchoscopic examination classification agreed with the final histopathological diagnosis) for biopsy as being moderate/severe dysplasia or worse.

and

-- the number of **lesions** accurately identified for biopsy as being moderate/severe dysplasia or worse.

For both methods of analysis, the three bronchoscopic classifications, defined above, were collapsed into 2 groups. Lesions classified as Class I and II by bronchoscopy examination were collapsed into the bronchospically negative group and the lesions classified as Class III were placed in the bronchoscopically positive group. Histologically positive lesions are defined as moderate/severe dysplasia or worse.

<u>Patient-Based Analysis</u>

173 patients were enrolled in Part II of the clinical study of the Xillix LIFE-Lung Fluorescence Endoscopy System. Of the 75 (43.3% of total) patients who had one or more histologically positive lesions on biopsy, 56 (75%) were correctly identified for biopsy by the WLB+fluoresence exam versus 28 (37%) patients correctly identifed by WLB alone. The increased number of patients correctly identifed for biopsy is reflected in an increased sensitivity from 0.37 for WLB to 0.75 for WLB+fluorescence. The complete statistical analysis is presented in the following table.

Data Summary Table (based on 173 patients)

	WLB	WLB plus Fluorescence
Sensitivity	0.37	0.75
Specificity	0.78	0.42
Positive Predictive Value (PPV)	0.56	0.50
Negative Predictive Value (NPV)	0.62	0.68
False Positive Rate	0.22	0.58

These results indicate that while there were additional negative biopsies taken when using the Xillix system, i.e. decreased specificity; fewer true positive patients were missed, i.e. increased sensitivity during this trial.

Of note is that, in a separate analysis, 19 patients classified as bronchoscopically negative by WLB+fluorescence were actually determined to be histologically positive by biopsy (false negatives). This compares to 47 false negatives with WLB alone. This analysis was performed on random biopsies of "negative" sites. Therefore, one cannot assume the absence of significant disease despite a bronchoscopically negative WLB+fluorescence examination.

Lesion-Based Analysis

700 evaluable lesions were derived from Part II of the Xillix study. Of the 95 lesions identified by WLB+fluorescence as requiring biopsy which were then confirmed as histopathologic positives only 35 of those lesions were identifiable using white light alone. The sensitivity increased by 0.42 (from .25 to .67). Please see complete data set presented in the following table.

Summary of the data (based on 700 biopsy lesions.)

	WLB	WLB plus Fluoresence
Sensitivity	0.25	0.67
Specificity	0.90	0.66
Positive Predictive Value (PPV)	0.39	0.33
Negative Predictive Value (NPV)	0.83	0.89
False Positive rate	0.10	0.34

These results indicate that there was a decrease in the positive predictive value associated with the addition of the Xillix System. The additional 196 biopsies taken as a result of the fluorescence exam yielded an additional 60 histologically proven positive biopsies.

Gender-based analysis

Sensitivity of the Xillix system in males was 0.68 and in females was 0.64.There was no statisitically significant difference between the gender-based cohorts indicating that the device was equally effective for both gender groups.

The study subjects ranged in age from 36 years to 87 years with a mean age of 62 years. One hundred ten patients (64%) were 60 years of age or older. These numbers are consistent with lung cancer prevelance data from ACS. There was no indication that the device was any more or less effective in any age group.

Patients in this study were not stratified by race. Figures from ACS do not show a statistically significant disease prevalence difference according to race. Based upon the device technology, there is no reason to anticipate that racial makeup would influence the safety or effectiveness of the Xillix System.

Conclusion of Clinical Study

The clinical investigation conducted with the Xillix LIFE-Lung Fluorescence Endoscopy System, used as an adjunct to white light bronchoscopy, demonstrated that the Xillix device plus white light bronchoscopy can enhance the physician's ability versus white light alone to identify and locate bronchial tissue suspicious for moderate/severe dysplasia or worse, for biopsy and histologic evaluation in appropriate patient populations. This device has been demonstrated safe and effective when used as indicated.